REMARKS

Claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, and 78-104 were previously pending and under examination. Claim 56 has been amended to recite "B-cell malignancy" and "comprising a backbone modification" and remove recitation of cancer. Support for this amendment is found at least on page 11, lines 12-28 and page 38, lines 16-18. No new matter has been added.

Drawings

Applicant acknowledges that the drawings filed on January 2, 2002 have been accepted.

Rejections Under 35 U.S.C. § 112, First Paragraph

Rejection Under 35 U.S.C. § 112, first paragraph, written description

The Examiner rejected claim 56 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Examiner, the rejection is that of a new matter rejection based on the recitation of "administering to the human a human or humanized antibody of IgG1 isotype which binds to CD19, CD20, CD22 antigen" (see Office Action, page 5).

Applicant respectfully disagrees and submits that the specification supports amended claim 56 at least as follows. Amended claim 56 recites:

> *administering to the human a human or humanized antibody of IgG1 isotype, which antibody binds to the surface antigen,*

Support for this recitation can be found in the specification at least on page 4, lines 5-9: "a method for treating cancer in a human by administering to a human an immunostimulatory nucleic acid and an antibody of IgG1 isotype (an IgG1 isotype antibody as used herein refers to a human or humanized IgG1 unless otherwise specified), which binds to a cell surface antigen of a cancer cell and wherein the nucleic acid and the antibody are administered in an effective amount for killing the cancer cell." Further, it is disclosed that the immunostimulatory nucleic acids are administered in combination with antibodies which specifically bind to cancer cell

surface antigens. The combination of immunostimulatory nucleic acids and human antibodies of the IgG1 isotype results in an increased survival rate (see page 13, lines 19-20). As disclosed in the specification, an antibody of IgG1 isotype refers to a human or humanized IgG1 which binds to a cell surface antigen of a cancer cell. Antibodies which bind to a cell surface antigen of a cancer cell are disclosed as anti-CD20 antibodies, anti-CD19 antibodies and anti-CD22 antibodies among others (see specification page 21, lines 20-24): "The immunostimulatory nucleic acids are administered in combination with antibodies which specifically bind to cancer cell surface antigens. These antibodies include but are not limited to anti-CD20 antibodies, anti-CD40 antibodies, anti-CD19 antibodies, anti-CD22 antibodies...." Applicant has further provided information on the commercial availability of such antibodies (see pages 21-26, Table 1). Humanized antibodies are further described on page 27, line 4 to page 28, line 4 of the specification. Specific anti-IgG1 isotype antibodies are further provided in the specification on pages 29-32, Table 2. Applicant has therefore provided adequate written description for the recitation in amended claim 56 of a humanized antibody of IgG1 isotype which binds to a CD19, CD20, or CD22 antigen.

Accordingly, withdrawal of the rejection of claim 56 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, is respectfully requested.

The Examiner also rejected claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-91, 94-98 and 100-103 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant respectfully disagrees. Applicant has discovered and disclosed immunostimulatory properties of nucleic acids that are defined by a common structural feature, a CpG motif. Applicant teaches that the immunostimulatory nucleic acids are capable of upregulating cell surface antigens and when combined with an antibody against such cell surface

antigens provide a means of treating disorders such as B-cell malignancies. According to *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Dir. 1996) "If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if [not] every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met." Further, "One shows that one is 'in possession' of *the invention* by describing the *invention* with all its claimed limitations, not that which makes it obvious" and "One does that by such descriptive means as words, structures, figures, diagrams, formulas etc., that fully set forth the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997). Applicant has provided an adequate written description for the group of CpG immunostimulatory nucleic acids claimed.

The Examiner has cited *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc., v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 for holding that adequate written description requires more than a mere statement that it is part of the invention but that the compound itself is required (see Office Action, page 8). However Applicant asserts that the present application and claims are distinguished from the issues raised in each of these cases for the following reasons. *Amgen Inc., v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 concerned a patent that included claims to all possible DNA encoding sequences that have activity resembling that of the specific DNA sequence encoding the erythropoietin protein, but the Applicant had disclosed only a single specific DNA sequence of erythropoietin having a specific activity. Similarly, *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) concerned claims in an interference which purported to cover all DNAs that code for a specific human protein (human fibroblast beta-interferon). The court held that claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. The present application is distinguished from both *Fiers v. Revel* and *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* because Applicant is not claiming nucleic acid sequence variations for a single disclosed protein but is instead claiming a class of CpG immunostimulatory nucleic acids having a common motif (CpG) and common property (ability

to increase the expression of surface antigens). CpG immunostimulatory nucleic acids are a class of nucleic acids that are recognized by those of ordinary skill in the art as evidenced by the numerous publications in this field.

Further, as disclosed in *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), *cert denied*; 502 U.S. 856 (1989) "[I]t is not necessary that a patent applicant test all the embodiments of his invention....; what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought." Applicant has disclosed a group of CpG immunostimulatory nucleic acids and has presented several hundred nucleic acid sequences having the CpG motif and has taught that such CpG nucleic acids are capable of increasing surface antigens on B cells. One of ordinary skill in the art knows how to make CpG nucleic acids and the present application provides sufficient disclosure of methods for using such nucleic acids. Applicant asserts therefore that adequate written description is provided for the immunostimulatory nucleic acid sequences of the claims.

Accordingly, withdrawal of the rejection of claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43,56, 78-91, 94-98, and 100-103 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, is respectfully requested.

Rejection Under 35 U.S.C. § 112, first paragraph, enablement

The Examiner rejected claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43,56, 78-91, 94-98, and 100-103 under 35 U.S.C. § 112, first paragraph, allegedly for not reasonably providing enablement for the entire scope of the instant claims. According to the Examiner, the specification is enabling for a method for inhibiting the growth of a B-cell malignancy, said method comprising administering to a subject having the B-cell malignancy: a) administering an immunostimulatory nucleic acid sequence to the subject in an amount effective to upregulate expression of CD20, CD19 or CD22 surface antigen in cancer cells of the B-cell malignancy wherein the immunostimulatory nucleic acid sequence is SEQ ID NO:729 and wherein the

immunostimulatory nucleic acid sequence comprises an unmethylated CpG motif and wherein the nucleic acid sequence further comprises a backbone modification; and b) an antibody specific for the surface antigen which is upregulated in response to administration of the immunostimulatory oligonucleotide; wherein administration of the immunostimulatory nucleic acid and the antibody results in the inhibition of the growth of the B-cell malignancy (see Office Action, page 9).

Applicant respectfully disagrees and asserts that the Examiner has not made a *prima facie* case for lack of enablement. The standard for enablement is undue experimentation as discussed in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). The Examiner has presented an analysis of the factors described in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988), each of which is addressed in turn herein.

Nature of the Invention and Breadth of the Claims

Applicant agrees with the Examiner's statement and asserts that the claims are not overly broad.

The Unpredictability of the Art and the State of the Prior Art

The Examiner has cited references each of which is addressed in turn herein.

Krieg, BioDrugs, 1998, 5:341-346

The Examiner has cited Krieg as teaching:

> "Synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by 5-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity."

Applicant does not disagree with this statement. The present claims recite an immunostimulatory CpG oligonucleotide between 6 and 100 (i.e. from 8 to 30 nucleotides or more), wherein the C of the CpG motif is unmethylated. Applicant has further demonstrated that

the immunostimulatory CpG oligonucleotide identified as CpG ODN 2006 having a CpG dinucleotide and being 24 nucleotides long (see page 71, lines 11-12) increases CD20 expression in B-CLLs and marginal zone lymphomas (see page 74, lines 20-21). Krieg *et al.* is not in disagreement with this disclosure.

Agrawal et al., Trends in Mol. Med., 2002, 8:114-121

Agrawal *et al.* is cited as teaching:

"The optimal motif for recognition by human immune cells is GTCGTT or TTCGTT"

According to the Examiner, this statement indicates variability in the efficacy in the immunostimulatory oligonucleotides encompassed by the claims (see Office Action, page 11). Applicant respectfully disagrees that this statement implies this. Agrawal *et al.* are merely disclosing that this particular motif was found to be the optimal motif for recognition by human immune cells and this statement does not discount other immunostimulatory oligonucleotides that do not include this motif could be equally or more effective. Agrawal *et al.* further discloses that the sequences flanking the CpG oligonucleotide also play a role in the induction of immunostimulatory activity and that in general the CpG dinucleotides that are preceded by a C or followed by a G stimulate lower cell responses (see page 114, right column, third paragraph).

Further, Agrawal is a review article summarizing numerous studies performed on CpG oligonucleotides and their effects on immune stimulation and potential use as therapeutics. Agrawal has described the therapeutic potential and utility of CpG DNA in human systems, including the use for treating cancer. A significant amount of discussion in Agrawal is directed to the production of second-generation immunostimulatory DNA that do not include CpG motifs. Although Agrawal recognizes that production of specific cytokines can be optimized by using specific CpG motifs with flanking sequences as well as dose and route of administration, Agrawal does not suggest that CpG DNA is not useful therapeutically. A demonstration that molecules can be optimized is not evidence that the invention as a whole is unpredictable. On page 116 Agrawal describes CpG in clinical trials and states that "Significant progress has been made in understanding the immunological and pharmacological affects of the first-generation

CpG DNA molecules." (Second column, third paragraph). Agrawal concludes by stating that "it is evident that CpG DNA is a powerful tool to modulate the immune system and can be exploited to treat a wide variety of diseases quite economically. Studies on the medicinal chemistry of CpG DNA have just begun and the preliminary results indicate several possible ways of further fine-tuning the immunomodulatory affects of first-generation CpG DNA by introducing site-specific chemical modifications." (see page 199, 2nd column, 2nd paragraph). There is no teaching in the disclosure of Agrawal *et al.* that other motifs are not immunostimulatory.

Furthermore, Agrawal's statement regarding optimization is not relevant for an enablement rejection because optimization is not the standard for enablement. CpG nucleic acids are a well recognized class of molecules having specific immunostimulatory properties. Agrawal further demonstrates the recognition in the field of these CpG nucleic acids and refers to the nucleic acids disclosed in the references as CpG oligonucleotides. The art is therefore familiar with such immunostimulatory nucleic acids.

Hartmann et al., J. Immunology, 2000, 164:1617-1624

Hartmann *et al.* is cited as teaching:

> "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the nonbridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN."

The statement referred to in this reference concerns issues related to FDA approval rather than enablement. As the MPEP states "[c]ourts have repeatedly found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use..... satisfies the utility requirement." MPEP § 2107.01 at page 2100-25, column 2. This standard also applies to enablement. *See* MPEP § 2164.06(a) (referring to §§ 2107-2107.03). The issue of safety of a drug is determined by the FDA not the PTO. *Id.* at p2100-26.

Working Examples and Guidance in the Specification

The Examiner has relied on the teachings of Agrawal *et al.* to imply that the disclosed example demonstrating the upregulation of the expression of CD19, CD20 and CD22 in malignant human B-cells in response to CpG ODN 2006 would not indicate that the oligonucleotide disclosed as ODN 1826 would have the same result, and further that no examples or guidance is disclosed indicating that the method is useful for treating any kind of cancer other than B-cell malignancies.

Applicant respectfully disagrees. There is no requirement that Applicant provide a working example for each and every embodiment of the claims. According to the MPEP § 2164.02 "A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled" "The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure". Further, "lack of working examples or lack of evidence that the claimed invention works should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement" (see MPEP § 2164.02).

Quantity of Experimentation

According to the Examiner, one of ordinary skill in the art would be required to perform additional experimentation in order to be able to effectively use the invention to the full scope of the claims (see Office Action, page 13).

Applicant respectfully disagrees that an undue quantity of experimentation would be required. The quantity of experimentation needed to be performed by one of ordinary skill in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. According to the MPEP § 2164.06 " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine...'" *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). The production of

nucleic acid molecules is routine and known by those of ordinary skill in the art. Methods are known in the art for synthesizing oligonucleotides containing a CpG motif. Oligonucleotides can be purchased from numerous commercial sources known to those of ordinary skill in the art. The oligonucleotide once synthesized could be administered to a subject having a B-cell malignancy. Applicant has provided the specific antigens whose expression is increased in response to such oligonucleotides. One of ordinary skill in the art need only test for an increase in the specified antigens using routine methods. No undue experimentation is required.

The Examiner further states that one would have to show how a nucleic acid comprising an unmethylated CpG motif, but without backbone modification could function as an immunostimulatory molecule. Without agreeing with the Examiner's position, Applicant has amended claim 56 to recite a backbone modification. Accordingly, Applicant submits that this point is obviated.

Level of Skill in the Art

Applicant maintains that a person of ordinary skill in the art would know how to perform the invention using experimental procedures that would be considered routine.

Accordingly, withdrawal of the rejection of claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43,56, 78-91, 94-98, and 100-103 under 35 U.S.C. § 112, first paragraph, allegedly for not reasonably providing enablement, is respectfully requested.

Claim Objections

Claims 92, 93, 99 and 104 were objected to as being dependent upon a rejected base claim. Applicant acknowledges that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. However, Applicant submits that the arguments provided above regarding claims 1, 24, 34, and 43, from which these claims depend, are sufficient to overcome this objection.

CONCLUSION

Applicant respectfully requests reconsideration. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the application in condition for allowance.

A check in the amount of $1,050.00 is enclosed to cover the three month extension of time fee. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825, under Docket No. C1039.70052US00.

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Respectfully submitted,

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